REMARKS

Claims 1 to 32 are pending in the application.

Claims 1, 2, 5, and 6 are canceled.

Claims 3, 4, 7 to 10, 13, 14, 18, 20 to 27, and 29 to 32 are currently amended.

Claims 11, 12, 15 to 17, 19, and 28 are original.

Claims 3, 4, and 7 to 32 would be all of the claims pending in the application if the instant amendment is entered.

Discussion of Amendments

Claims 3, 7, 8, and 9 are currently amended to recite subject matter that was previously incorporated by reference from claim 1 and to correct a typographical error by replacing "piperadinyl" with "piperidinyl" in the definitions of R_C, R_D, R_E, R_F, R_I, R_J, R_K, R_L and R_M. Claim 4 is currently amended to delete the phrase "any other nerve injury between the peripheral nerve system and the central nerve system". Claims 10, 13, 14, 18, 20 to 27, and 29 to 32 are currently amended to depend from claim 8 instead of claim 1, as claim 1 is canceled.

Election/Restriction

Applicants note with appreciation that all the claims are examined in view of their traversal and remarks regarding the restriction requirement of record.

Double Patenting Rejection

Claims 1 to 5 and 7 to 32 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 24 to 33 and 39 of U.S. Patent No. 6,469,004. Although the identified claims are not identical, it was alleged in the Office Action that they are not patentably distinct from each other because the '004 patent teaches the method of treating arthritis, organ transplantation, and diabetes complication.

Applicants respectfully traverse this rejection on the grounds that claims 1, 2, and 5 are canceled, rendering rejection of claims 1, 2, and 5 moot, and that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c), a statement under 37 C.F.R. § 3.73(b), and a copy of an assignment in support thereof, are being filed concurrently herewith.

Applicants affirm that the filing of the terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and should not be deemed to raise a presumption or estoppel on the merits of the rejection. (*Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991)).

In view of the above remarks, Applicants believe that claims 1 to 5 and 7 to 32 are patentable under the judicially created doctrine of obviousness-type double patenting.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1 to 6 and 10 to 32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for arthritis, pain associated with uremia, and post-operative pain, allegedly does not provide enablement for other chronic pains. Particularly, it was alleged in the Office Action that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims without undue experimentation.

In the Office Action, eight factors to consider when assessing if a disclosure would have required undue experimentation were cited from *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). The eight factors recited in the Office Action were:

1. The quantity of experimentation necessary,
2. The amount of direction or guidance provided,
3. The presence or absence of working examples,
4. The nature of the invention,
5. The state of the prior art,
6. The relative skill of those in the art,
7. The predictability of the art, and
8. The breadth of the claims.

Reasoning for the rejection based on the eight factors was then presented. It was alleged in the Office Action that the quantity of experimentation is enormous since the claimed method encompasses treatments of all kinds of chronic pain. It was further alleged in the Office Action that the amount of direction or guidance provided was not sufficient since different chronic pains would have distinct pathophysiology or unknown pathophysiology. On this basis it was argued that the skilled artisan would not have known what chronic pain conditions could be treated by the compounds described in claim 3.

It was also alleged that the presence of working examples is limited: only a few chronic pain conditions are described in the working examples out of all the known chronic pain conditions. Relying on the allegation that different chronic pains would allegedly have distinct pathophysiology or unknown pathophysiology, it was further argued that there is no known relationship between the MEK pathway and various chronic pain conditions. Thus, even though it was admitted in the Office Action that the level of skill in the art is high, it was alleged that it is unlikely that the compounds described in claim 3 would be able to treat [every] chronic pain known to man.

Applicants respectfully traverse the rejection on the grounds that (1) claims 1, 2, 5, and 6 are canceled, and claims 10 to 32 now depend from claim 8

instead of from claim 1, rendering rejection of claims 1, 2, 5, 6, and 10 to 32 moot, and (2) that Applicants believe that the skilled artisan may practice the invention of claims 3 and 4 without undue experimentation for the reasons provided below.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue" (MPEP 2164.01 under the heading UNDUE EXPERIMENTATION). Further, the experimentation can be complex but not undue, because the art typically engages in such experimentation (MPEP 2164.01 under the heading UNDUE EXPERIMENTATION). Still further, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976).

The invention of claim 3 is directed to treating chronic pain that is a type of neuropathic pain. Claim 4, which depends from claim 3, is directed to treating chronic pain that is a type of neuropathic pain, wherein the neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, and arthritis pain, inclusively.

It is believed by those skilled in the art that neuropathic pain results from an abnormality in a nerve pathway that disrupts nerve signals, which in turn are abnormally interpreted in the brain (page 1, lines 10 to 11 of the specification).

Biological Examples 1 to 3 of the specification describe in vivo models of chronic neuropathic pain that are characterized by static allodynia. Biological Example 1 describes a diabetic static allodynia model of neuropathic pain induced by injection of streptozocin. Biological Examples 2 and 3 describe a diabetic static allodynia model of neuropathic pain of a chronic constriction injury (CCI) type.

Biological Examples 1 and 2 describe use of the MEK inhibitor PD 198306, which is not a compound of Formula (I) as described in claim 3. Biological Example 3 describes use of the MEK inhibitor PD 184352, which also is not a compound of Formula (I) as described in claim 3, and the MEK inhibitor PD 254552, which is a compound of Formula (I) described in claim 3. As shown in Biological Examples 1, 2, and/or 3, PD 198306, PD 184352, and PD254552 each were found to alleviate chronic neuropathic pain.

Biological Example 3 also describes intrathecal administration of MEK inhibitors PD219622 or PD 297447, which are not compounds of Formula (I) as described in claim 3. While PD219622 or PD 297447 did not appear to exhibit statistically significant chronic neuropathic pain alleviating activity in the experiment, it cannot be scientifically concluded that these compounds would not be effective in treating chronic neuropathic pain, as administration of PD219622 or PD 297447 at higher doses or for longer periods of time may produce a statistically significant chronic neuropathic pain alleviating effect.

Thus, the data presented in Biological Examples 1 to 3 of the specification demonstrate that MEK inhibitors in general, and a compound of Formula (I) as described in claim 3 in particular, effectively alleviate chronic neuropathic pain.

This data supported Applicants' belief at the time of filing the present application that MEK inhibitors generally, and particularly the MEK inhibitors

that are compounds of Formula (I) as described in claim 3, are effective for treating chronic neuropathic pain (specification on page 1, at lines 7 to 31; on page 48, at lines 16 to 18; and original claim 4 on page 76, at lines 16 to 18).

Applicants also believed that efficacy of compounds of Formula (I) as described in claim 3 for treating neuropathic pain correlated with the compounds' relative affinities for MEK (page 48, lines 16 to 19 of the specification). Binding affinities for the compounds of Formula (I) as described in claim 3 may be readily determined as described in U.S. Patent No. 6,649,004 B1, which was cited in the Office Action.

The specification references two literature articles in the prestigious journal, *Pain*, on page 46, at lines 23 to 28. These peer-reviewed articles describe the use of the in vivo models described in Biological Examples 1 to 3 for measuring chronic neuropathic pain alleviating effects of compounds. The first reference, Bennett GJ and Xie Y-K, discloses an in vivo neuropathic pain model that "produces disorders of pain sensation like those seen in man."

Further, Applicants believed at the time of filing the present application that correlations had been established between the in vitro affinities of compounds of Formula (I) as described in claim 3 and the in vivo efficacy of the compounds in neuropathic pain animal models, and, further, between that in vivo efficacy in animals and efficacy of the compounds for treating neuropathic type chronic pain seen in humans. Accordingly, Applicants believed a correlation existed between the in vitro binding affinities for MEK of compounds of Formula (I) as described in claim 3 and clinical efficacy of the compounds for treating chronic neuropathic pain in a human at the time of filing the present application.

Still further, the skill of the artisan is high and the artisan typically engages in clinical drug experimentation. Established methods for treating

neuropathic type chronic pain with gabapentin, for example, could guide the skilled artisan seeking to treat chronic neuropathic pain with a MEK inhibitor (page 2, at lines 6 to 8 of the specification). In view of the amount of direction or guidance in the specification as discussed above, it would thus have been merely routine experimentation for the skilled artisan to administer a compound of Formula (I) as described in claim 3 to a patient suffering from a particular neuropathic type chronic pain, and clinically evaluate the compound's pain-alleviating effects.

Accordingly, Applicants believe that any experimentation required to practice the invention of claims 3 or 4 would not be undue, and thus that claims 3 and 4, as well as claims 10 to 32, are patentable under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the Office Action, it was alleged that the limitation "any other nerve injury between the peripheral nerve system and the central nerve system" renders claim 4 indefinite because it is not clear what type of injury is encompassed by the claim and, as a result, it is not clear what chronic pain is encompassed by the claim.

Applicants respectfully traverse the rejection on the basis that claim 4 has been amended to delete the objected to phrase, rendering the rejection of claim 4 moot.

Conclusion

In view of the above amendments and remarks, Applicants believe that the rejections of claims 1 to 32 are overcome. Applicants request reconsideration and allowance of claims 3, 4, and 7 to 32.

Respectfully submitted,

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